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14. ABSTRACT

Some prostate cancers are very aggressive and progress to metastasis. Accumulating evidence suggests that the angiogenesis pathway may play a critical role for this aggressiveness. The significance of angiogenesis in prostate cancer is demonstrated by its correlation with Gleason score, clinical stage, progression, metastasis and survival. However, relatively few studies have assessed the role of genes involved in angiogenesis in recurrence of prostate cancer after radiotherapy. On the basis of strong biological rationale, we propose to comprehensively study this pathway in a well-characterized cohort of prostate cancer cases. Our hypothesis is that genetic and epigenetic individual variation in angiogenesis genes is associated with recurrence of prostate cancer after radiotherapy. We will test this hypothesis with a systematic evaluation of the 82 key genes in the angiogenesis pathway with recurrence of prostate cancer. The ultimate goal of this study is to identify biomarkers that can be used at the time of diagnosis to predict risk of recurrence and improve clinical treatment decision making.

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Introduction

Most prostate cancer progresses relatively slowly. However, some cases grow aggressively and metastasize through the bloodstream and lymphatic system to other parts of the body. The most important clinical challenge for prostate cancer is to determine which of these two clinical forms a patient is presenting with. This information is critically important given the significant morbidity associated with treatment interventions and could eventually help distinguish men who need intensive treatment from those who may be better served by watchful waiting.

The primary treatment options for initial therapy for localized prostate cancer are surgical treatment or radiotherapy. Radiation therapy (RT) shows several distinct advantages over radical prostatectomy. RT avoids complications from surgery as well as risks associated with anesthesia. Moreover, this therapy includes a low risk of urinary incontinence. Major disadvantage of external beam RT include a treatment course of 8-9 weeks. -50% of patients have some temporary bladder or bowel symptoms during treatment. There is a risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time. Brachytherapy, another type of RT, involves placing radioactive sources into the prostate tissue. Disadvantages of this treatment include the risk of acute urinary retention. Up to this point, clinical variables, such as the level of PSA, clinical stage and the Gleason score are used to estimate prognosis and inform treatment modalities [1-3]. Although they are extremely useful, more biomarkers are needed to increase accuracy the outcome of prostate cancer.

Accumulating evidence suggests that the angiogenesis pathway may play a critical role. The significance of angiogenesis in prostate cancer is demonstrated by its correlation with Gleason score, clinical stage, progression, metastasis and survival [4-9]. However, relatively few studies have assessed the role of angiogenesis genes in recurrence of prostate cancer after radiotherapy. Research to identify the specific genes and genetic variations relevant to angiogenesis risk among prostate cancer patients with radiation therapy remain largely unexplored. Part of the reason why previous results have been inconclusive may be that a major source of genetic regulation has been ignored: gene silencing through epigenetics. On the basis of strong biological rationale, we proposed to comprehensively study this pathway in a well-characterized cohort of prostate cancer cases. Our hypothesis is that genetic and epigenetic individual variation in angiogenesis genes is associated with recurrence of prostate cancer after radiotherapy. We tested this hypothesis with a systematic evaluation of the key genes in the angiogenesis pathway with recurrence of prostate cancer. The ultimate goal of this study is to identify biomarkers that can be used at the time of diagnosis to predict risk of recurrence and improve clinical treatment decision making.

Body

Task 1: Since we submitted a progress report in 2013, we further identified and confirmed 1211 prostate cancer patients, who had a treatment between 2004 and 2012 at Moffitt Cancer Center. Among these patients, 367 patients were treated with radiation as a primary option. Clinical and demographic information of these patients were collected (Table 1).

Table 1. Characteristics of prostate cancer patients

Variables	value	N (%)
Treatment	Radiation	367 (30.3)
	Surgery	323 (26.7)
	Hormone	157 (13.0)
	Watching waiting	364 (30.1)
Gleason score	2-6	662 (56.3)
	7	401 (34.1)

	8-10	113 (9.6)
Age at diagnosis	years	64.3 ± 8.4
Race	White	1024 (84.6)
	Black	119 (9.8)
	Others	68 (5.6)
Family History	Y	335 (39.5)
	N	849 (60.5)

Task 2: To evaluate role of genetic variations in progression of prostate cancer, we used public data base and extensive literature search to identify candidate SNPs from 82 angiogenesis related genes which show significant differential expression in prostate tumor tissue, and selected 1,500 SNPs in these 82 genes using the binning algorithm based on linkage disequilibrium. Since the 2013 progress report, 200 DNA samples from prostate cancer patients were prepared for genotyping. Genotyping was performed on these samples. Table 2 is the results from the initial analysis.

Table 2: Top 30 SNPs associated with aggressiveness of prostate cancer.

SNP	Chr.	Genes	OR 95%CI
rs3803236	13	COL4A2	1.11 (1.06-1.17)
rs7139621	13	COL4A2	1.1 (1.05-1.16)
rs1523303	2	TGFA	0.91 (0.86-0.96)
rs7605323	2	TGFA	0.9 (0.85-0.96)
rs7995461	13	COL4A2	1.1 (1.04-1.15)
rs1654513	19	KLK3:KLK2:	0.91 (0.86-0.96)
rs1433165	8	ANGPT1	1.09 (1.04-1.15)
rs9559814	13	COL4A2	1.09 (1.04-1.15)
rs4151437	13	RB1	1.2 (1.08-1.34)
rs1980059	8	ANGPT1	1.09 (1.03-1.15)
rs4773186	13	COL4A2	1.1 (1.04-1.16)
rs4773187	13	COL4A2	1.1 (1.04-1.16)
rs4148853	7	NOS3:ATG9B:	1.11 (1.04-1.18)
rs7994073	13	COL4A2	1.11 (1.04-1.18)
rs10255526	7	NOS3:ATG9B:	1.11 (1.04-1.18)
rs9555701	13	COL4A2	1.1 (1.04-1.18)
rs10245199	7	NOS3:ATG9B:	1.1 (1.03-1.16)
rs997476	4	NFKB1:MANBA	1.18 (1.06-1.31)
rs3803233	13	COL4A2	0.92 (0.88-0.97)
rs4252117	6	PLG	1.09 (1.03-1.15)
rs1041834	21	TMPRSS2	0.92 (0.87-0.97)
rs4252135	6	PLG	1.09 (1.03-1.15)
rs4252165	6	PLG	1.09 (1.03-1.15)
rs4252107	6	PLG	1.09 (1.03-1.15)
rs9521760	13	COL4A2	1.09 (1.03-1.15)
rs10489985	2	TGFA	0.91 (0.85-0.97)
rs783147	6	PLG	1.08 (1.03-1.14)
rs12483377	21	COL18A1:SLC19A1	0.87 (0.79-0.95)
rs11569033	4	EGF	0.73 (0.59-0.9)
rs7326449	13	COL4A2	1.1 (1.03-1.17)

Task 3: We will build prediction models based on these results with clinical variables.

Key Research Accomplishments since 2013 progress report

1. We constructed additional cohorts for prostate cancer patients who had radiation therapy between 2004-2012.
2. 367 additional prostate cancer patients with radiation therapy were identified.
3. Genotyping analysis for 200 DNA samples were performed.

Reportable Outcomes

Evaluation of prediction model will be presented in scientific conference, submitted to peer-reviewed scientific journals and reported in final report.

Conclusion

Current conclusion is that genetic variations in angiogenesis genes may influence risk for progression of prostate cancer.

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Appendices

None